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Review article

O-(2-[^{18}F]fluoroethyl)-L-tyrosine: uptake mechanisms and clinical applications

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Abstract

O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) is a promising tracer for PET that has demonstrated convincing results especially in the diagnostics of brain tumors. In contrast to other radiolabeled amino acids, it can be produced with high efficiency and distributed in a satellite concept like the widely used 2-[^{18}F]fluoro-2-deoxy-D-glucose. Although FET is not incorporated into proteins, it shows high uptake in cerebral gliomas and in extracranial squamous cell carcinomas owing to increased transport. The tracer exhibits high in vivo stability, low uptake in inflammatory tissue and suitable uptake kinetics for clinical imaging, which indicates that it may become a new standard tracer for PET. In this article, the present knowledge on the uptake mechanisms and the clinical applications of FET are reviewed and the clinical perspectives are discussed.

Keywords: *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine; Amino acid transport; Tumors; PET

1. Introduction

Radiolabeled amino acids are attracting increasing interest in nuclear medicine over the past years. Amino acids are accumulated in malignant transformed cells owing to increased expression of amino acid transporters. These substrates play not only an important role in protein synthesis, but also as precursors of hormones and neurotransmitters. In contrast to glucose derivatives, the uptake of amino acids in macrophages and other inflammatory cells is lower, so that amino acid tracers appear to be more specific than, for example, 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) for tumor imaging [1].

Many amino acids have been radiolabeled to study potential imaging characteristics. These radiolabeled amino acids differ in ease of synthesis, biodistribution and formation of metabolites in vivo. To date, the most frequently used amino acid tracers are [^{11}C-methyl]-L-methionine (MET) for PET and 3-[^{123}I]iodo-α-methyl-L-tyrosine (IMT) for SPECT [2]. Due to the short physical half-life of the ^{11}C-label (20.38 min), MET PET remains restricted to a few PET centers with a cyclotron on site and could not be established in routine clinical practice despite convincing first clinical results. IMT SPECT offers a more widespread application [3], but the spatial resolution of SPECT is considerably lower than that of PET. Therefore, a number of attempts have been undertaken to label amino acids with ^{18}F (109.7 min half-life), but the yield of the radiosynthesis of these ^{18}F-labeled amino acids was rather ineffective [4,5].

O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) (Fig. 1) is one of the first ^{18}F-labeled amino acids that can be produced in large amounts for clinical purposes and is applicable for PET studies in a satellite concept similar to the widely used FDG [6,7].

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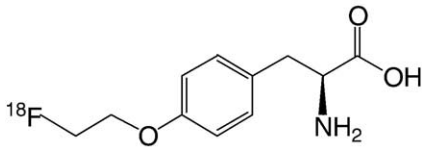

Fig. 1. (2-[^{18}F]fluoroethyl)-L-tyrosine.

Although this amino acid is not incorporated into proteins, uptake by tumor cells is stereospecific and mediated by amino acid transporters [6,8]. Furthermore, it has been shown in animal experiments that FET in contrast to MET and FDG exhibits low uptake in nonneoplastic inflammatory cells and in inflammatory lymph nodes, which promises a high specificity for the detection of tumor cells [9,20]. Meanwhile, a number of studies have investigated the clinical application of FET in brain tumors and extracranial malignancies. In parallel, animal experiments and in vitro studies have been undertaken to shed light into the transport and uptake mechanisms of FET. In this article, the present knowledge of the uptake mechanisms and the clinical applications of FET are reviewed and the clinical perspectives discussed.

2. Radiosynthesis

Generally, two distinct synthesis methods are applied for routine production of FET. A two-step reaction of FET synthesis is based on the ^{18}F-fluoroalkylation of the disodium salt of L-tyrosine [6]. In the first step, [^{18}F]fluoroethyltosylate is produced via no-carrier-added nucleophilic ^{18}F-fluorination of 1.2-bistosyloxyethane with subsequent reversed-phase HPLC purification and on-line fixation of the ^{18}F-fluoroalkylation reagent. The ^{18}F-fluoroalkylation step is performed in presence of the disodium salt of L-tyrosine in DMSO at 90°C. After HPLC purification combined with solid-phase extraction and formulation, FET can be obtained with an overall radiochemical yield of about 40% within approximately 60-min synthesis time. The disadvantage of this two-step reaction is the difficulty of automation and the necessity of two HPLC-purification steps.

An alternative route to FET is the direct-phase transfer-mediated nucleophilic ^{18}F-fluorination of N-protected *O*-(2-tosyloxyethyl)-L-tyrosine ester with subsequent deprotection. The no-carrier-added ^{18}F-fluorination of *N*-trityl-*O*-(2-tosyloxyethyl)-L-tyrosine tert-butylester with subsequent deprotection under nonaqueous conditions is an efficient method to produce the radiotracer with uncorrected radiochemical yields up to 40% useful for the distribution according to the satellite concept [7]. Deprotection of the intermediate FET derivative is performed in presence of trifluoroacetic acid in trichloromethane followed by solid-phase extraction. The FET containing HPLC eluent can be used directly for human application. The radiochemical purity is >98% and the specific activity measured at the end of synthesis is >200 GBq/μmol.

3. Toxicity

In general, FET is nontoxic, and no side effects have been reported in the literature and were not observed in more than 400 diagnostic applications of the tracer at our institution. The toxicity of the compound has been tested in mice after a single intravenous injection (tail vein) of doses up to 150 μg/kg body weight for a period of 15 days (Research and Consulting Company Itingen/Switzerland, Project 666887). No animal died due to the administration of the test substance. During the administration period, no behavioral abnormalities were observed. At necropsy, no specific gross findings were detected. Thus, FET was well tolerated in mice in doses up to 150 μg/kg body weight, that is, LD_{50} values are higher than 150 μg/kg body weight. In humans, a dose of maximally 400 MBq FET is injected. At a specific activity of >200 GBq/μmol, which is routinely achieved in our center and given the molecular weight of 227 g/mol, this corresponds to less than 0.45 μg FET per patient resp. 6.5 ng FET/kg body weight.

4. Metabolism

A number of studies suggest that increased uptake of FET in tumors is owing to transport phenomena and that FET does not participate in specific metabolic pathways such as catecholamine metabolism.

Since the pancreatic gland produces large amounts of secretory proteins it is a representative organ to detect an incorporation of artificial radiolabeled amino acids into proteins. Interestingly, FET exhibited a high accumulation in the pancreas of mice [6], but whole-body scans in humans demonstrated only a low uptake of FET in the pancreas [11]. The reason for this species difference remains unclear, but it appears to be caused by differences in transport characteristics rather than by differences in protein synthesis between the pancreas of humans and mice. L-[^{11}C]tyrosine, for example, which is incorporated into proteins, also shows intensive uptake in the human pancreas [2].

Dissection experiments in mice proved that 60 min after injection of FET, radioactivity in homogenized pancreas, brain and tumor tissue was not precipitable by trichloroacetic acid and was completely eluted in the low-molecular-weight fraction [6]. In addition, FET showed no protein incorporation in F98 rat glioma cells, while for MET a 15% protein incorporation after 2-h incubation time was noted [3].

Since L-tyrosine, the natural parent of FET, is a biologically important substrate not only for synthesis of proteins and thyroid hormones, but also as precursor for the synthesis of catecholamines and of melanin after hydroxylation, a role of FET in such pathways might be considered in principle. However, no significant accumulation of FET in the adrenal glands could be identified [11], which make a significant incorporation of FET in the catecholamine pathway very unlikely. An incorporation of FET into the melanin pathway has not yet been investigated. If FET